Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants

Pollution from Personal Actions

Christian G. Daughton, Ph.D.

Chief, Environmental Chemistry Branch

Environmental Sciences Division

National Exposure Research Laboratory

Office of Research and Development

Environmental Protection Agency

Las Vegas, Nevada 89119

daughton.christian@epa.gov

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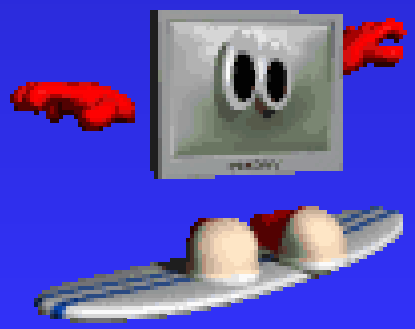
NOTE

Because of the size of this presentation, this file comprises only the 4th (and last) part of the entire PPCPs slide presentation. The other parts must be accessed separately.

These slides and many additional materials are available at the U.S. EPA's ***PPCPs Web Site***:

http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm



The Future for Research on PPCPs in the Environment

- Poorly characterized ramifications of PPCPs in the environment (occurrence, fate, transport, effects) warrant a more precautionary view on their environmental disposition.

- A portion of the effort that continues to be invested in elucidating the environmental transformation and fate of POPs/PBTs might be better redirected to PPCPs.

- One area that should be pursued immediately is a search of the literature for unintended, unexpected effects, especially related to aquatic organisms, with some emphasis on efflux pump inhibitors/promoters.

Near-term actions to minimize introduction of drugs to environment or their potential effects

- **Screening for EPI Potential:** Develop new aquatic testing procedures (esp. cellular based); evaluate possible impacts of potent, new-generation efflux pump inhibitors (EPIs).

- **Environmental "Friendliness"**: Factor environmental proclivity into PPCP design/marketing "green" PPCPs: maximize biodegradability/photolability to innocuous end products, minimize therapeutic dose ("calibrated dosing"), emphasize single-enantiomeric (homo-chiral) drugs.

- **Drug Prescribing & Use**: Better inform physicians (and public) to environmental consequences of over-prescribing medications — minimize misuse/overuse. Engage medical community to develop guidelines. Identify pathogens prior to prescribing antibiotics ("imprudent use").

continued -

Near-term actions (cont'd)

- **Internet Dispensing**: Educate/encourage the pharmacy community to understand environmental consequences of over-dispensing (and dispensing without a prescription) to minimize unneeded drug use and attendant disposal [see: www.fda.gov/oc/buyonline].

- **Individualization of Therapy**: Encourage drug manufacturers to provide medical community with the necessary information to tailor drug dosages to the individual (esp. long-term maintenance drugs) on basis of body weight, age, sex, health status, subtle genetic distinctions, and known individual drug sensitivities — individualization of therapy. Identify lowest effective dosages ("calibrated dosing").

continued -

Near-term actions (cont'd)

- **Develop alternative delivery mechanisms**: Reduce dosages with (1) new routes for existing and new drugs (e.g., inhalable, dermal), (2) new formulations (e.g., for insoluble drugs - ca. 30% of USP drugs and 50% of prospective drugs are poorly water-soluble), and (3) new mechanisms for delivery of drugs to the target (e.g., antibody-linked drugs).

continued -

Near-term actions (cont'd)

- **Expand exploration of non-chemical alternatives to traditional medications.** Examples include:

Reducing/eliminating drug dosages by use of placebos [e.g., see refs at: "Medicinal Mimicry: Sometimes, placebos work—but how?" D. Christensen, *Science News* 3 Feb. 2001, 159(5), 74-75,78; http://www.sciencenews.org/20010203/bob1ref.asp].

Use of probiotics to block pathogen adhesion (as post-surgical, prophylactic antibiotic) [e.g., see: Reid, G. et al. *Trends Microbiol.* 2001, 9(9), 424-8; Harder, B. *Science News* 2002, 161(5), 72-74, http://www.sciencenews.org/20020202/bob9.asp] and the use of "competitive exclusion (CE) cultures" in veterinary medicine to lessen antibiotic use (the sole CE approved to date by the U.S. FDA is PREEMPT, in 1998).

continued -

Near-term actions (cont'd)

- **Consider reducing package sizes of PPCPs:** Some PPCPs are perhaps more prone to being disposed because they are prescribed or purchased in quantities too great to be used before expiration or because they tend to expire more rapidly.

- **Encourage patient compliance:** Noncompliance by the patient can result in prescribed courses of a particular drug to accumulate, leading to the expired/unused dosages to be disposed in the domestic sewage system.

- **Lessen drug abuse** (consumption of more frequent/higher doses than prescribed or use of illicit drugs) to reduce excretion.

- **Reduce need for disposal** by reducing prescribed/purchased quantities too great to be used before expiration, or increasing shelf life.

continued -

Near-term actions (cont'd)

- **Proper Disposal**: Better inform pharmacy industry to provide proper disposal instructions to end-user for unused/expired drugs. Better guidance for disposition of non-controlled substances by disposal companies. Consider implementing Extended Producer Responsibility (EPR).

- **Importance of Individuals' Actions**: Educate public on (i) how their individual actions each contributes to burden of PPCPs in the environment, (ii) how PPCPs can possibly affect aquatic biota, and (iii) the advantages accrued by conscientious/responsible disposal and usage of PPCPs.

continued -

Near-term actions (cont'd)

- **Use of Drugs as Environmental Markers of Sewage**: Capitalize on occurrence of certain, more easily degraded PPCPs to serve as conservative markers/tracers of discharge (early warning) of raw (or insufficiently treated) sewage.
- **Source Separation for Domestic Wastes:** Advancement in, and implementation of, new technologies for dealing with waste at the source (e.g., separation of streams) holds the highest potential for the future minimization of waste flows to the environment. Toilet re-engineering is but one example; for example, see: http://www.novaquatis.eawag.ch/

continued -

Near-term actions (cont'd)

- **Expand ecotox considerations for new drug classes:** Of potential high importance is the possible need to more closely evaluate potential ecological effects from the pending introduction of new drug classes. A currently evolving example is that of the angiogenesis inhibitors.

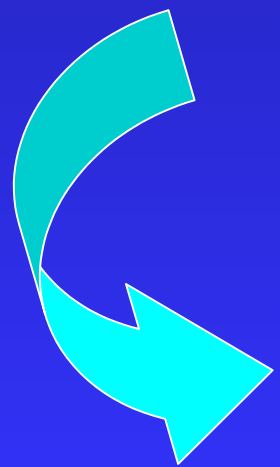
[overview at: http://www.students.stedwards.edu/~ehouran/intro.html/]

This broad therapeutic class has a number of synthetics – both legacy drugs, such as thalidomide, and many new ones. These compounds have profound teratogenic potential (thalidomide being a well-known example), but little is known with respect to aquatic organisms.

- concluded -

Summary Distillation of the Significance of PPCPs in the Environment

Using the "risk assessment paradigm" as an organizing framework, we can consider the factors of pollutant source, occurrence/exposure, effects, and pollution prevention, and encapsulate the overall issue of PPCPs in the environment as follows:



Summary — 1 — PPCP Sources

All chemicals applied externally or ingested (and their bioactive transformation products) have potential to be excreted/washed into sewage systems and from there discharged to the aquatic/terrestrial environments. Input to the environment is a function of the efficiency of human absorption/metabolism and the efficiency of the treatment technologies employed (if any). Efficiencies vary from chemical to chemical and between sewage treatment facilities. Obviously, discharge of untreated sewage maximizes occurrence of PPCPs in the environment.

- **Non-Point Sources**: Importance of dispersed, diffuse, non-point "discharges" of anthropogenic chemicals to environment has been overshadowed for decades by the more obvious point sources.

- **Importance of Individual Action**: Importance and significance of individuals in directly contributing to the combined load of chemicals in environment has been largely overlooked.

- **"Connectedness"**: PPCPs illustrate immediate, intimate, & inseparable connection of the actions/activities of the individual with environment.

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Summary — 2 — Occurrence/Exposure

An extraordinarily limited subset of tens of thousands of commerce/industrial chemicals has been the narrow focus of environmental chemists for decades.

- **The Larger Puzzle**: Consideration of PPCPs as an additional class of long-ignored chemicals in exposure would contribute to the larger risk assessment puzzle and lend more perspective in the quest for "holistic" risk assessments.

- **Toxicity Out of Context**: Environmental toxicologists are usually forced to look at exposure issues "out of context" because of the extreme complexity of factoring in exposure from all potential toxicants that may be present in any given exposure situation (and the lack of comprehensive chemical analysis data).

- **Limited View of Persistence**: Our view of pollutant "persistence" might not be sufficiently encompassing being that the continual introduction of PPCPs to the aquatic environment via sewage outfalls could potentially lead to continual exposure even though a pollutant may not be truly "persistent".

- **Aquatic Exposure the Major Concern:** Exposure risks for aquatic organisms are much larger than those for humans, given much lower potential concentrations in upgraded (treated) domestic drinking water and the fact that aquatic organisms suffer continual, multi-generational exposures to any chemical in their domain.

continued -

Summary — 3 — Effects

Drugs are purposefully designed to interact with cellular receptors at low concentrations and to elicit specific biological effects. Unintended adverse effects can also occur from interaction with non-target receptors.

- **Traditional Toxicology**: Environmental toxicology has long focused on the more obvious, acute effects of exposure.

- **Shift of Focus to Subtle Effects**: Any concern with PPCPs in the environment (and if/when present, they would be expected to be at very low concentrations) points to the need for development of tests that detect more subtle end-points (neurobehavioral effects and inhibition of efflux pumps being two examples).

- **Little data:** While sparse aquatic/terrestrial toxicology data exists for PPCPs, the little that has been published shows the potential for subtle effects (that could escape our immediate attention) at low concentrations.

- **Antibiotics:** Of course, more obvious consequences are actively being debated, such as the promotion of antibiotic resistance in pathogens from the (over?)use of antimicrobials in people, animals, and agriculture.

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Summary — 4 — Pollution Prevention

Pollution prevention is preferable to remediation

Proactive vs. Reactive approaches

- **Central Importance of the Individual**: In closing the loop (from pollution prevention back to source), the most overlooked key to minimizing environmental pollution is the importance of the individual — including the user/consumer and the prescribing/dispensing professional communities.

- **Actions to Consider:** A variety of actions can be considered by all involved (including manufacturers) to minimize society's use of PPCPs while still accruing full benefit from these largely useful, beneficial, and often extremely important chemicals. Importance of "Extended Product Responsibility".

- concluded -

"Take-Home" Message

PPCPs in the environment mirror its direct connection with human activities and actions

- By reducing the consumption and disposal of PPCPs, benefits could accrue to both humans and to the environment.
- The reduction in use of types and quantities (e.g., dosages) of antibiotics and other drugs could reduce side effects and lessen the likelihood of pathogen resistance development.
- "Calibrated dosing" and more enlightened disposal methods would lessen the burden of PPCPs on the environment.

continued -

So What ?!?

In the absence of definitive environmental or human health effects data resulting from actual exposure to environmental levels (which, after all, are far below therapeutic dosages) why should we be concerned ?

While drugs might occur in domestic potable waters at extremely low concentrations, we must be wary of dismissing the toxicological significance for humans (or aquatic life) of low concentrations (ppt) of drugs in drinking water on the sole basis that such concentrations are orders of magnitude lower than the therapeutic dosages (amounting to merely nanograms-per-day intakes via drinking water). This remains a common assertion in prognostications of potential minimal human health effects (or absence of) and is potentially flawed for any number of the following reasons…

continued -

... because ...

Several issues are not considered by this supposition…

- Epidemiological studies ascribing effects to common pollutants (e.g., PBTs) rarely factor in exposure to other, non-conventional pollutants (because they are not measured or considered in these studies)

Role of co-pollutants in morbidity/mortality studies is commonly ignored.

Because of the vast complexities faced by epidemiologists, only a limited subset of pollutants is usually considered.

Leads to unrecognized confounding of conclusions regarding associations.

Perhaps other pollutants (known and yet-to-be identified) are more strongly associated.

continued -

... because ...

Several issues are not considered by this supposition…

- Recommended therapeutic dosages can be higher than the therapeutic dose actually required (a dual consequence of not adjusting doses set in clinical trials and of not individualizing therapy)
- Non-target, unintended effects can not be discounted at sub-therapeutic dosages (unintended effects can occur at lower concentrations than do therapeutic effects, especially during long-term maintenance therapy)
- Additive/synergistic effects from simultaneous consumption of numerous drugs are essentially unknown (intake of multiple drugs adds complexity of additional burden to patient already taking medications with low therapeutic indexes) – e.g., combined loading of individual anticholinergics or serotonin modulators

continued -

... because ...

- Continual, life-long exposure to trace levels — an unexplored domain of toxicology.

- Lack of trends data. Even where PPCP concentrations are currently low, no data sets exist for revealing long-term trends. For any particular PPCP at a given geographic location, is its concentration over time decreasing, remaining constant (steady state), or increasing?

Hypothesis regarding trends for PPCPs in the environment: Continually expanding uses and consumption of individual PPCPs points to concentrations of existing drugs increasing in addition to adding to the burden of discrete drug types in the environment. Will those PPCPs with longer half-lives tend to accumulate? Drug use can be expected to continue to rise due to a confluence of drivers: increased per capita consumption, expanding population, expanding potential markets (partly due to mainstream advertising/marketing), patent expirations (shift to less expensive generics), new target age groups, and new uses for existing drugs. Old therapeutics are being used not just for additional clinical conditions (those for which they were not originally developed) but also for non-disease states — for example, medical manipulation or alteration of personality traits and satisfaction of certain social needs — referred to as "cosmetic pharmacology."

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Importance of acquiring TRENDS data

- Acquisition of trends data for a suite of PPCPs (representatives from each of numerous significant classes), shown to recur amongst municipal STWs across the country, is of key importance.
- Trends data would prove critical if the current concentrations are below any known effects levels.
- A frequent criticism of the concern with this issue is that the limited data on environmental occurrence points to concentrations well below *therapeutic levels*. One of several limitations to this argument is that there are no data whatsoever that show whether what are currently trace concentrations are serving as a foundation on which more significant concentrations are slowly building — using trends data to predict well in advance the onset of effects levels.
- If environmental concentrations begin to trend upward, this could trigger renewed or expanded examinations or trigger more rigorous pollution prevention efforts. Both short-lived and long-lived PPCPs should be selected for trends monitoring.

continued -

... because ...

Finally, there are potential, intangible advantages in being proactive versus reactive …

- the **Precautionary Principle** – the principle of precautionary action (*also see sidebar*) that redistributes the burden of proof because the science required for truly and fully assessing risks lags far behind the requisite supporting science:

e.g., see links provided at:
http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#The Precautionary Principle

- concluded -

Sidebar: The **Precautionary Principle**

Factors Leading to the Precautionary Principle

Science (objective; data oriented) ⇒

quick and versed at delimiting with certainty what is **unknown**
slow but able to define what is **knowable**
poor at separating the **unknowable** from the unknown
incapable of removing all **uncertainty** (absolute current limitations of knowledge)

Science + Uncertainty can never yield Scientific Certainty

Science + Uncertainty + Policy/Political judgment ⇒ course of further study or action (subjective, value-oriented, emotional, but rational nonetheless in its approach)

Fusing science with Judgment is a balancing act designed to avoid:
actions based on "type I errors" (false alarms; false positives)
==> improperly taking action based on incorrect or insufficient data
inactions based on "type II errors" (failed alarms; overlooked significance)
==> not taking action when it was indeed warranted

For some comprehensive discussions on the Precautionary Principle, refer to:
http://www.epa.gov/nerlesd1/chemistry/ppcp/relevant.htm#The Precautionary Principle

Research Needs and Gaps for Assessing the Ultimate Importance of PPCPs as Environmental Pollutants

A wide array of research needs/gaps and other activities need to be addressed to delineate the scope and magnitude of environmental and human health issues derived from the occurrence of PPCPs in the environment. **In the remaining slides is presented a summary of some of the major needs/gaps arranged according to disciplines and according to the risk assessment paradigm**; no relative priorities are implied by their order of presentation. While this listing may not be comprehensive, it should provide researchers with ideas as to where efforts need to be invested.

(C.G. Daughton October 2001)

Research Needs and Gaps

A wide array of research needs/gaps and other activities need to be addressed to delineate the scope and magnitude of environmental and human health issues derived from the occurrence of PPCPs in the environment. Below is presented a summary of some of the major needs/gaps arranged according to disciplines and according to the risk assessment paradigm; no relative priorities are implied by their order of presentation. While this listing is in no way comprehensive, it should provide researchers with ideas as to where initial and continuing efforts need to be invested.

Research Needs and Gaps: Categories

- Research Coordination
- Sources/Origins
- Occurrence
- Fate/Transport
- Hydrology
- Analytical Chemistry
- Exposure
- Toxicology
- Medical
- Design/Manufacturing
- Engineering
- Control
- Prevention
- Risk Assessment/Regulation
- Public Outreach
- Fostering New Research/Research Planning

Needs and Gaps: PPCPs

Research Coordination

Beginning in the late 1990's, the pace of research continues to escalate -- but primarily with respect to the analytical chemistry and environmental occurrence of PPCPs. The proliferation of research, especially in Europe, Scandinavia, Canada, and the U.S., points to the urgent need for an internationally coordinated research strategy to minimize duplication of efforts and maximize the impact of limited research resources. The outline presented here could serve as a starting point for such a strategy.

Needs and Gaps: PPCPs

Sources/Origins

- Determine relative contributions to environmental loadings from direct disposal of unwanted PPCPs to sewage (and trash) vs. sewage (excretion and washing).
- Relative contributions from hospitals vs. municipal sewage.
- Relative contributions from confined animal feeding operations (CAFOs) vs. human use (esp. antibiotics).
- Relative contributions from straightpiping vs. treated sewage.
- Relative contributions of illicit vs. licit drugs.
- Possible importance of excipients.
- Need for nationwide database showing prescription/OTC sales data and usage (GIS).

Needs and Gaps: PPCPs

Occurrence

- Concentration, frequency, and geographic extent and distribution in sewage and aquatic systems need to be better defined on a national level (more monitoring - surface, ground, drinking).
- Significance of regional prescribing/usage differences.
- Significance of various sewage and drinking water treatment technology capabilities.
- Establish status and trends of individual PPCPs.
- Literature is silent regarding occurrence of many PPCPs. Is this because of an absence of data or a failure to report "data of absence"?

PPCPs in Municipal Sewage

- Important to recognize that ALL municipal sewage, regardless of location, will contain PPCPs. Issue is not unique to any particular municipal area.

- Each geographic area will differ only with respect to the types, quantities, and relative abundances of individual PPCPs.

PPCPs in Environment

- **Occurrence differences in**:

Raw sewage are a function of: **(i)** local prescribing and usage customs, **(ii)** confluence of hospitals, **(iii)** state policies and customs regarding disposal of unused PPCPs, and **(iv)** local manufacture and usage of illicit and abused drugs.

Surface and ground waters are a function of: **(i)** whether treatment technologies are employed (straightpiping, malfunctioning septic systems, overflow events), **(ii)** types of treatment technologies employed for sewage, potable water, or reinjection waters, and **(iii)** local/seasonal fluctuations in biophysicochemical transformation potential (e.g., biodegradation, photolysis).

Example BOTE Calculation for SSRIs in Sewage from a Major Municipal System

Facts:

Fluvoxamine elicits mussel spawning at 318 ng/L (see refs by Fong as cited by Daughton & Ternes 1999).

Example county population >1.25 million.

140 Mgal (530 ML) sewage processed per day.

Fluvoxamine, fluoxetine, and paroxetine are administered roughly in the 20-300 mg/day range.

Assumptions (simplistic, but realistic):

Average dosage regime of 50 mg/day for each of these three SSRIs (there are other SSRIs) (conservative assumption).

Only 2% of unaltered parent compound is excreted and SRSs (metabolites -- there are many) harbor 1/20th of the parent drugs' activities (realistic assumption).

One-tenth of population takes one of these three drugs (reasonable assumption).

No metabolism of SSRIs in STW (overly conservative assumption).

Total daily amount of SSRIs potentially introduced to an example county's receiving waters per day:

$1.25\backslash^{6}$ people X 10^{-1} X 50 mg/day-people X (0.02 mg active ingredient/mg parent ingredient + 0.98/20 active metabolite/mg parent ingredient) =

$1.25\backslash^{5}$ X 3.5 mg/day =

$4.4\backslash^{5}$ mg/day => $4.4\backslash^{5}$ mg/day X 530^{-1} day/ML = $8.3\backslash^{2}$ mg/ML X 10^{-6} ML/L = $8.3\backslash^{-4}$ mg/L =

⇨ **0.83 µg/L (ca. 1 ppb) in treated effluent**

This exceeds the amount of fluvoxamine required for effects in mussels, but is probably less than the amount required for the other SSRIs. Combined effects from other SSRIs have not been considered here. This in only one of many effects that have been noted for shellfish (which, while not relevant to some aquatic locales, is merely meant to be illustrative for sewage discharges).

Needs and Gaps: PPCPs

Fate/Transport

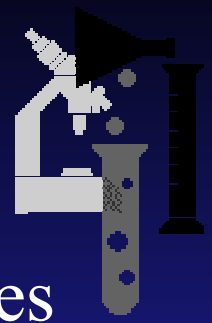
- Identify potential for formation of bioactive metabolites and other transformation products.
- Establish major environmental degradation mechanisms (biological, physicochemical).

Needs and Gaps: PPCPs

Hydrology

- Better understanding of transport to and degradation in groundwater.
- Groundwater recharge (accidental and purposeful); significance regarding recycling of contaminants.
- Need for consistent, national guidance regarding composition of active recharge waters. What level of treatment should be required? Tailor to local geology.

Needs and Gaps: PPCPs

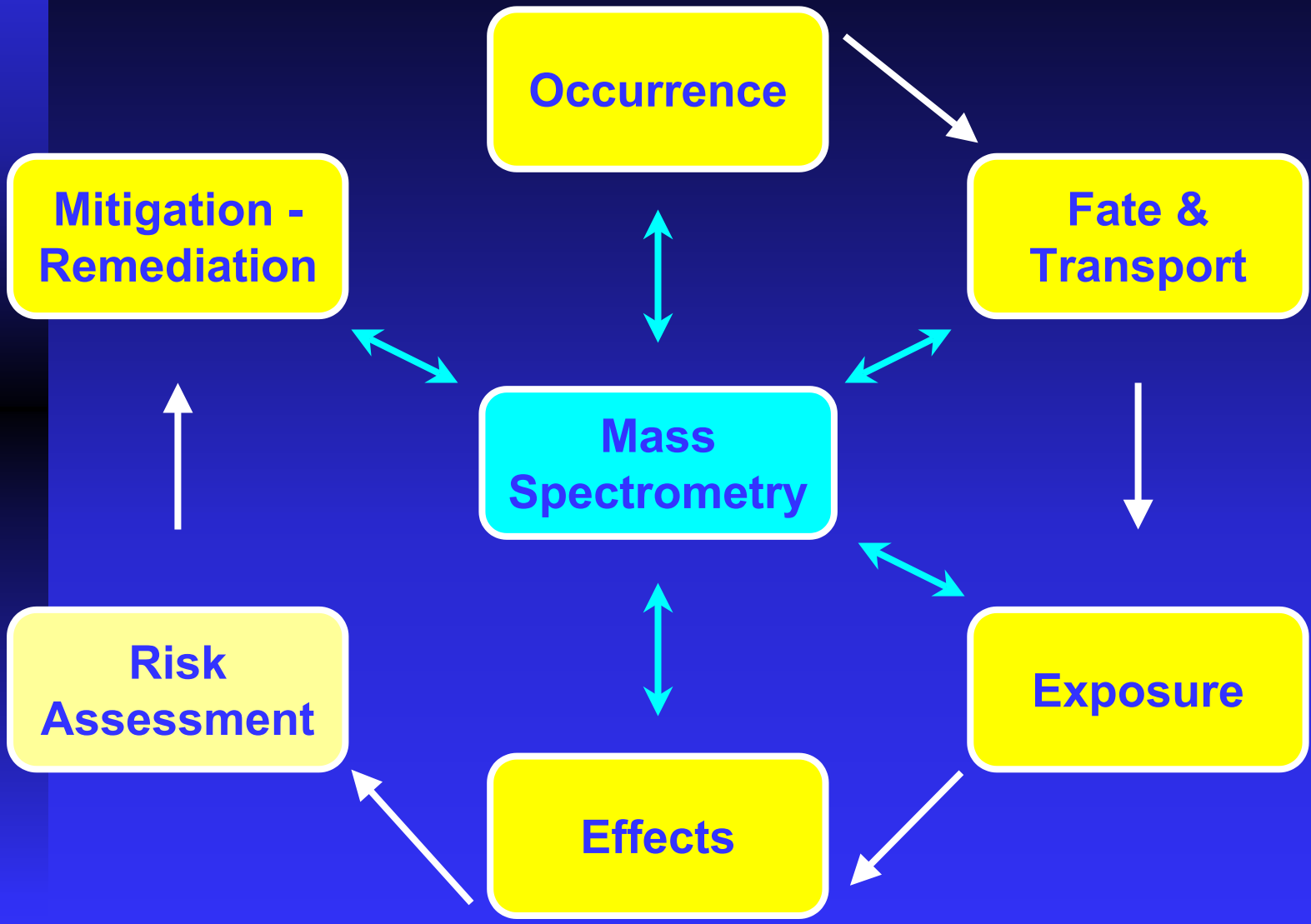


Analytical Chemistry

- Need for enrichment and detection methodologies for compounds more polar than environmental chemists are used to dealing with.
- Facilitate more widespread and efficient implementation of non-target monitoring approaches (e.g., for emerging pollutants – those that were not anticipated or expected).

- Importance of establishing a nationwide monitoring network to detect all NEWLY present (emerging) chemicals in waterways (including PPCPs).

Mass Spectrometry and the Risk Paradigm



C.G. Daughton, U.S. EPA, NERL, Las Vegas, NV

February 2001

Imperative of Quality-Assured Data

Every chemical structural identification must be confirmed by comparison using a certified reference standard for:

(1) **chromatographic retention time**, and

(2) **mass spectrum**.

Reliance solely on mass spectral matching using electronic libraries alone can yield erroneous identifications.

Interpretive mass spectrometry often plays an important role. Especially when reference standards are not available or cannot be synthesized.

Side-Bar: The Imperative for a Nationwide Approach to Identifying Emerging, Nascent Chemical Risks

- Chemicals that have not previously existed in the environment, but which are just beginning to develop or "emerge," present unknown risks, some of which cannot be anticipated.
- Historical approach to identifying and controlling chemical risks is **reactive**.
- Environmental regulators have traditionally approached chemical pollution by devoting resources solely to managing established, well-characterized risks --- "list-based", target-analyte monitoring.
- **Proactive** approach is needed to **preventing** the establishment of new risks so that their management would not be needed.
- New and unanticipated chemicals (together with their transformation products) that have not previously occurred in the environment need to be identified as early as possible — **well before their becoming pervasive in the environment --- NON-target analyte approach**.

continued -

Side-Bar: One Proposal for a Nationwide Approach to Identifying Emerging, Nascent Chemical Risks

"Pollutant Fingerprint Anomalies"

(C.G. Daughton, 29 August 2001)

http://www.epa.gov/nerlesd1/chemistry/pharma/science-issues.htm#One Proposal

- Develop repertoire of highly reproducible chromatographic/ electrophoretic separations methods coupled with a sensitive, universal detector (e.g., any of various mass spectrometric formats).

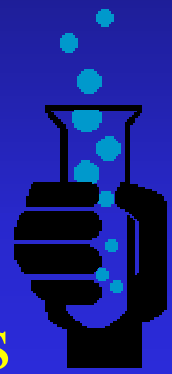
- Periodically screen aqueous samples from nation-wide locations (representative of urban, rural, and pristine areas) for **existence of any NEW constituent – ignoring all those that are normally present** (a type of "chemical amnesty" for the purposes of focusing resources on new pollutants).

- Approach would require sample-concentration schemes capable of multi-orders-of-magnitude "enrichment" of solutes, regardless of their polarities. The organic constituents in the resulting extracts would then be subjected to appropriate separation schemes, yielding reproducible "fingerprints" that reflect the compounds present and their relative abundances.

- concluded -

PPCPs as Analytical Tools

Primary concern regarding PPCPs in the environment is their presence as pollutants (with ultimate questions related to human and eco health consequences).



Their very existence as environmental contaminants, however, provides a number of opportunities for accomplishing other purposes unrelated to any concern regarding their occurrence as pollutants -- as tools for probing or measuring other, unrelated environmental factors.

continued -

PPCPs as Analytical Tools

Two characteristics of PPCPs distinguish them from other anthropogenic chemicals and give them unique capabilities for use as tools:

(1) Individual PPCPs or their metabolites in the environment result solely from human (or domestic animal) ingestion or use.

(2) Each PPCP has a well-known date of introduction to commerce (generally a function of FDA approval). Some also have dates of withdrawal from commerce.

continued -

PPCPs as Analytical Tools

Sentinels of Sewage Intrusion: Use of PPCPs in natural waters as "tracers", "markers", "indicators", "sentinels", or "early warning" of environmental contamination by human sewage or animal excrement is an idea that has garnered significant attention.

This idea capitalizes on the relative ease and speed of chemically analyzing water samples to determine the occurrence of PPCPs with a spectrum of half-lives, as opposed to cumbersome measurement of pathogens.

continued -

PPCPs as Analytical Tools

Social Science Tool: The use of sewage-influent monitoring for illicit drugs has been proposed as a non-intrusive means of more accurately assessing the extent of illicit drug usage on a community-wide scale -- without revealing any information regarding usage by individuals. This idea was first proposed by Daughton (2001).

continued -

PPCPs as Analytical Tools

Geologic "Dating": PPCPs could possibly be used as a means of providing maximum "ages" for ground waters or sediments with respect to the most recent intrusion of contaminated surface waters. Since all PPCPs have a well-established date of introduction to the commercial, consumer market (and some have exit dates) their presence/absence has the potential to be used as dating tools for establishing maximum ages.

continued -

PPCPs as Analytical Tools

Geologic "Dating" (con't): This approach could possibly work with any parent compound or transformation product with sufficient persistence in the groundwater environment.

PPCPs (especially drugs) have the distinct advantage over other tracers being that their commercial debuts (and dates of market exit) are well defined and can even be established for particular geographic locales (on the basis of regional prescription use). Dates could be bracketed by using drugs with different commercialization dates.

- concluded -

Needs and Gaps: PPCPs

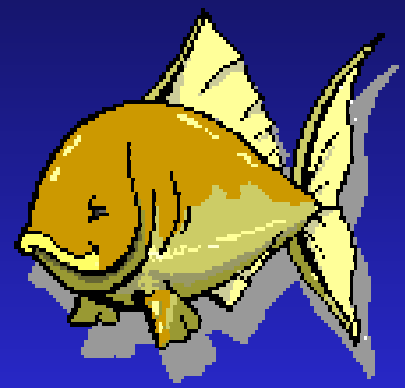
Exposure

- Determine significance of chronic, long-term exposure via drinking water and foods (fin/shell fish) to multiple chemicals (at low, ng/L concentrations).

- Define the potential toxicological significance of each individual therapeutic/use class. Currently most is known only regarding **antibiotics** and **estrogenic steroids**.

Aquatic organisms — captive to continual, life-cycle chemical exposures

- Aquatic Exposure is Key: Any chemical introduced via sewage to the aquatic realm can lead to continual, multigenerational exposure for aquatic organisms.



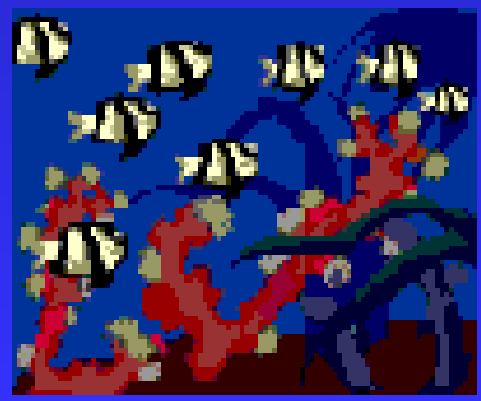
Re-evaluation of "Persistence": Chemicals continually infused to the aquatic environment essentially become "persistent" pollutants even if their half-lives are short — their supply is continually replenished (analogous to a bacterial chemostat). These can be referred to as ***pseudo-persistent*** **chemicals (P2's)**.

Critical Importance of Aquatic Environment

- Aquatic Exposure is Key: Probably more the 80% of Earth's organisms exist only in aquatic ecosystems.

- Sentinels: Many aquatic species are key bioindicators that portend the health of the biosphere.

- But historic focus is on terrestrial mammals: The perceived relevance of terrestrial mammalian toxicology retards the advancement of aquatic toxicology.



Needs and Gaps: PPCPs

Toxicology

- Better elucidate effects issues associated with multiple exposures: additive effects, interactions (synergism/antagonism), exposure duration (e.g., multi-generational), windows of exposure vulnerability, and aggregate, cumulative, complementary exposures.
- Elucidate importance of low-level effects (e.g., nM-pM, sub-ppb/ppt), hormesis, and paradoxical dose-response.
- Determine importance of efflux pumps as first line of defense for aquatic organisms.

continued -

Needs and Gaps: PPCPs

Toxicology (con't)

- Expand understanding of non-target effects (esp. for non-target organisms).
- Improve ecotoxicological testing (e.g., accommodate for more subtle effects and endpoints not currently measured; e.g., long-onset, latent damage; subtle shifts in behavior or intelligence).
- Expand ecotoxicological considerations for accommodating mechanisms or modes of action (e.g., angiogenesis inhibitors, efflux pump inhibitors).

- concluded -

Effects studies (aquatic and human) need to proceed via three fronts:

(1) Significant effects that are unique to each therapeutic class (e.g., resistance-selection for antibiotics). Evaluate class by class.

(2) Significant effects that are mediated via highly conserved biochemical features and pathways across taxa and which are elicited across multiple therapeutic classes. Examples include efflux pumps and specific signaling pathways (e.g., serotonin).

(3) Interactions between chemical stressors and cascade effects within cells.

Needs and Gaps: PPCPs

Medical

- Individualization of therapy (e.g., proactive "calibrated dosing") to minimize dosing.
- Minimize overuse, misuse, imprudent use (involves patient education as well).
- Expand exploration of non-chemical alternatives to traditional medications (e.g., reducing/eliminating drug dosages by use of placebos).

Needs and Gaps: PPCPs

Design/Manufacturing

- Aim for "environmental friendliness" (green design and innocuous fate).
- Accelerate development of better drug-delivery systems and formulations (e.g., inhalable, dermal, to minimize dosage).
- Accelerate development of enantiomeric drugs (*see next slide*).

Synthesis Origin and Chiral Distribution of Discrete Drugs Worldwide

numbers of discrete drugs in each category

source	Achiral	Chiral		*worldwide totals*
		Racemic	**Single Enantiomer**	
natural (or derived analog)	6	8	509	523
synthetic	799	467	61	1327
worldwide totals	805	475	570	1850

adapted from: W. Locke "Modern Drug Discovery," *The Alchemist*, 19 January 2001; available: http://www.chemweb.com/alchem/articles/985883680391.html

Needs and Gaps: PPCPs

Engineering

- Delineate the factors that determine the susceptibility of PPCPs to biological sewage treatment.
- Develop inexpensive alterations to sewage plant treatment technologies to control refractory PPCPs.
- Ensure that RO for groundwater recharge is reliable (and then treating the brine for enriched contaminants).

continued -

Needs and Gaps: PPCPs

Engineering

- **Wastewater Treatment Research Targeted at PPCPs**

Among the research projects on PPCPs supported by the EU are three that are coordinated as the "PHARMA-cluster". These projects are aimed at developing advanced monitoring and removal technologies for both human and veterinary pharmaceuticals:

continued -

Needs and Gaps: PPCPs

Engineering

Wastewater Treatment Research Targeted at PPCPs

- **EU-Project Poseidon**

"Assessment of Technologies for the Removal of Pharmaceuticals and Personal Care Products in Sewage and Drinking Water Facilities to Improve the Indirect Potable Water Reuse"
http://www.poseidon.geo.uni-mainz.de/index.htm
http://www.poseidon.geo.uni-mainz.de/the_objectives.htm

- **REMPHARMAWATER**

"Ecotoxicological assessments and removal technologies for pharmaceuticals in wastewaters"
http://cds.unina.it/%7Ermarotta/

- **ERAVMIS**

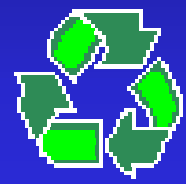
"Environmental risk assessment of veterinary medicines in sludge"
http://www.oieau.fr/5pcrd/projets/ERAVMIS.htm

- concluded -

Needs and Gaps: PPCPs

Control

- Disposal: Standardized set of national regulations for disposal of unwanted, expired PPCPs (public, state, and medical, e.g., nursing homes, physician samples).
- Implement "Extended Producer Responsibility" (EPR) (e.g., manufacturers and distributors).
- Outreach efforts for heightening public awareness for recycling alternatives (e.g., reverse distributors).



- Source separation for domestic wastes: New technologies for dealing with waste at the source (e.g., separation of streams). Toilet re-engineering is but one example.
- Continue nationwide elimination of straightpiping and septic systems; also overflow events.

Needs and Gaps: PPCPs

Prevention

- Proactive vs. Reactive.
- Encouragement for purchase of only needed amounts of PPCPs (e.g., package sizes conducive to avoiding expiration).
- Reduce over-dispensing and black market sales of drugs (e.g., "Internet pharmacies").
- Expand use of "drug mining" (e.g., hospital reclamation of highly toxic drugs from excreta and other wastes).
- Expand use of "reverse distributors".

Needs and Gaps: PPCPs

Risk Assessment/Regulation

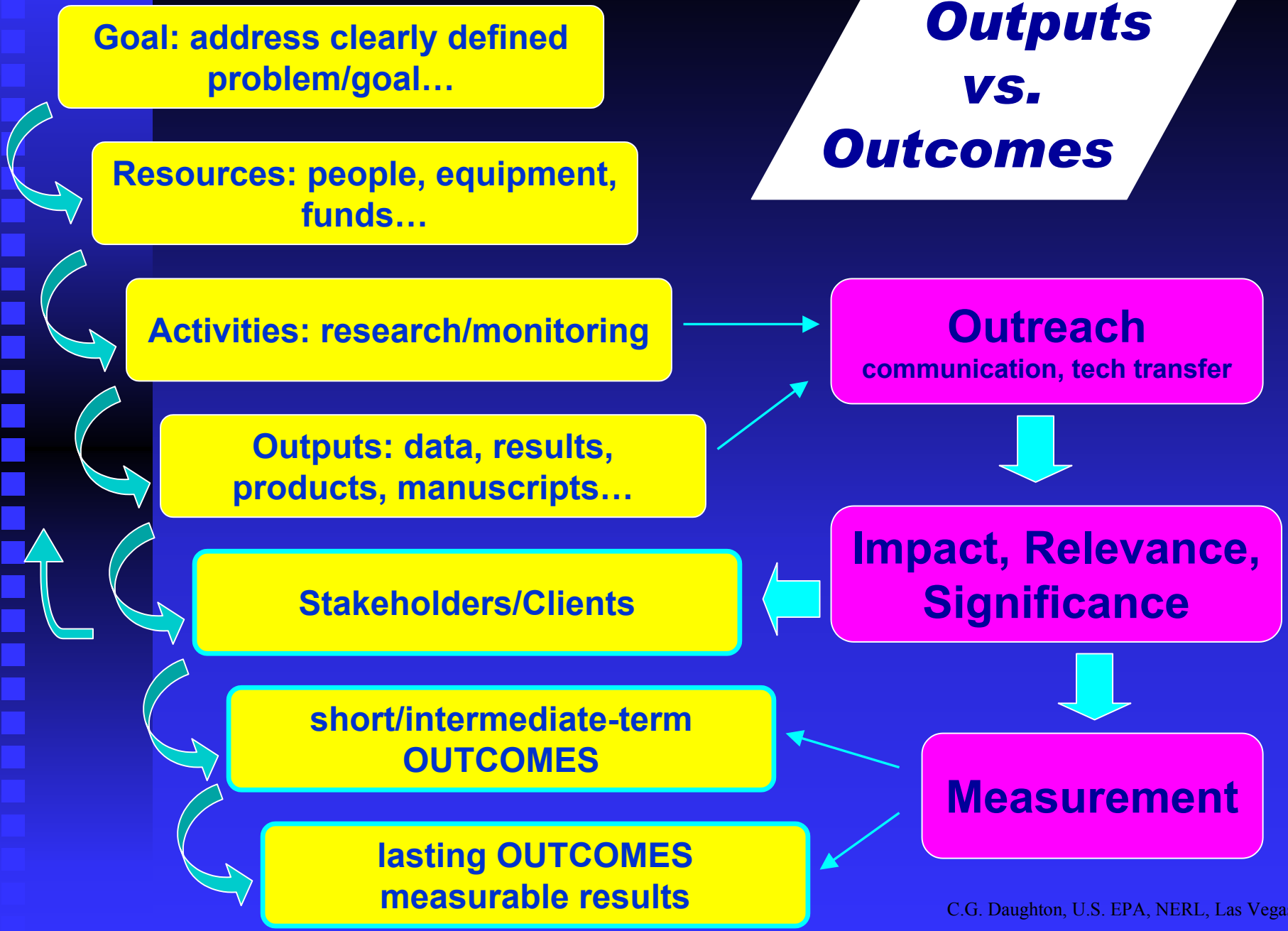
- Impart better understanding that traditional assessments accommodate only a small portion of the universe of chemicals to which humans and organisms are exposed. For example, what is the importance of the conventional pollutants (e.g., PBTs) versus all other agents.
- Expand understanding that chemical stability per se is not a prerequisite for "persistence" in the environment.
- Accumulate occurrence data for EPA's Contaminate Chemical List (CCL, see: http://www.epa.gov/safewater/ucmr.html).
- Ensure that new knowledge is assimilated in new regulations.

Needs and Gaps: PPCPs

Public Outreach

- Recognition that POPs and PBTs represent only a portion of the overall environmental pollutant load.
- Show the health benefits of minimizing overuse/misuse of drugs (e.g., antibiotics).
- Capitalize on occurrence/effects issues to increase public understanding and appreciation for environmental science. Tie actions of the individual to environmental consequences.
- Create materials for public education (esp. via the web).
- Use of drug monitoring to raise community awareness of local usage (esp. illicit/abused drugs).
- Use of drug monitoring to raise community awareness of inadvertent financial support to terrorism.

Outputs vs. Outcomes



C.G. Daughton, U.S. EPA, NERL, Las Vegas, NV

February 2001

Needs and Gaps: PPCPs

Fostering New Research/Research Planning

- Catalyze and promote further exploration, discussion, and collaboration on emerging pollutants by all stakeholders.
- Develop formal interagency workgroup to develop cohesive plan for PPCPs (and emerging pollutants).
- Organize national/international conferences devoted to specific issues under the overall topic.

Proposal: Interagency Strategy for "Emerging Contaminants"

Development of Interagency Emerging-Contaminants Research/Monitoring Strategy

PPCPs provide opportunity for science community to be proactive/collaborative.

Need to coordinate activities from wide array of government agencies, public entities, private organizations, and other stakeholders. Accommodate varied interests and perspectives.

Ultimate Objective: Design and implement an early warning system for any new chemical contaminant – whether naturally occurring or anthropogenic.

Near-Term Objective: Develop cohesive, unified strategy for determining risks of ambient PPCPs to wildlife and humans.

Near-Term Implementation: ***2003 Workshop on PPCPs***. Senior science representatives and central coordinators from major federal entities, including CDC, DOI (USFWS), EPA, FDA, NIH, and USGS. Later workshops would involve other entities, such as states, public/private granting organizations, manufacturers/distributors, regulators.

Workshop Product: ***Framework for Development of a National PPCPs Coordination Strategy.***

A Postscript

The Fragmentation of Science - Loss of the Bigger Picture
Critical Importance of *Knowledge "Mining"* and *Synthesis*

Much of the world's published science literature is vastly underutilized and highly fragmented. With respect to environmental aspects of PPCPs, the medical literature in particular has yet to be effectively utilized to address ecological effects questions.

While the information available in any research field continues to grow exponentially, proportionately less time is devoted in trying to "mine" and capture this knowledge to synthesize a larger picture.

Literature is often ignored or simply becomes "lost" to future investigators. The paradoxical message is that the published literature is not as important as "new" findings.

Duplication of effort and reinvention of the wheel are symptoms of the failure to pay sufficient attention to the literature.

A parallel problem is that the larger picture remains obscure when the literature is not critically examined, especially for issues that cross multiple disciplines.

Solutions to problems and answers to questions can be waiting to be "discovered" amidst research that has already been reported.

continued -

Postscript (continued)

This problem relates in part to the fact that there is little professional reward in attempting to distill, synthesize, and integrate what is known about a topic. Science managers tend to value publication of "original" data — even if it is incremental, and even, unbeknownst them, if it is merely "rediscovered" data.

Furthermore, scientists often do not understand the significance, impact, or relevance of their work because they are caught in the drive to publish — at the expense of reading, comprehending, distilling, synthesizing, and communicating.

The issue of "capture and synthesis" of fragmented knowledge has been discussed by Prof. Peter Csermely (Semmelweis University, Budapest) in "Limits of Science Growth" (4 June 1999, *Science*, Science's Compass, pp. 1622-23): Csermely argues that little attention is being paid to the fragmentation of the world's science literature. This is a major reason that it is so extremely difficult for individual scientists to have a broad-based appreciation for the "bigger picture". Csermely writes: "**There is only a limited effort to achieve the appropriate balance between the discovery of new facts and finding their proper place and importance in the framework of science**." This relates partly to what can be referred to as understanding the "significance", "impact", or "relevance" of one's work. Csermely goes on to note that **"science itself is not self-integrating, and there are fewer and fewer people taking responsibility for net-making". "Integration [of knowledge] needs time and patience..." "...greater credit should be given to those who make serious attempts to integrate their findings into the whole of human knowledge."**

Postscript (concluded)

More extensive discussions of this topic are available under the topic of "Literature Forensics: Use and Misuse of Published Literature" and can be accessed at:

http://www.epa.gov/nerlesd1/chemistry/forensics.htm

Final Perspective
The Role of the Scientist

In Bruce Alberts' *2000 President's Address* to the National Academy of Sciences ("Science and Human Needs"), he addresses in part "the responsibilities of scientists" with the following words, which lend further, and final, perspective on the ideas presented in this discussion (available at: http://www.nas.edu).

"... (B)ecause political will is often short term, and misinformation about science abounds, we scientists ourselves must become much more engaged in the everyday life of our governments and our communities." As 'civic scientists', "...in the 21st century, science and scientists will be judged on how well they help solve local and world problems, not only on how well they generate new knowledge. The impact of our research is everywhere, and we must step out and make sure that our work is understood and appropriately used by the world. ...We also need to be explicit about what is not known, and be clear about the questions that science cannot answer."

Declining Science Knowledge of General Public: A Responsibility of Scientists?

Survey of adults conducted by California Academy of Sciences and Harris Interactive Polling†:

- 53% did not know Earth revolves around Sun
- 48% had no sense of percentage of Earth's surface covered by water (ca. 70%)
- 42% did not know whether humans co-existed with dinosaurs

1 in 5 adults could not answer any of these questions. Little more than 1 in 3 college graduates answered all three correctly.

Profound national knowledge gap at time when a democratic discussion of many, complex technical issues is critical for our future.

Poll also indicated that the public most trusts (65%) scientists to convey needed information about the natural world. The public (95%) is extremely interested in learning about the environment.

While a strong desire to learn about science and to take actions to protect the environment are evident, fewer than 1 in 5 felt sufficiently knowledgeable to take any action.

Clearly a responsibility rests with scientists to better communicate the meaning, significance, and impact of their work -- in clearly articulated terms.

† **http://www.calacademy.org/geninfo/newsroom/releases/survey_results.htm** (March 2001)

Declining Science Knowledge of General Public: A Responsibility of Scientists?

More extensive discussions of this topic are available under the topic of "**Communicating Science & Science Literacy** " and can be accessed at:

http://www.epa.gov/nerlesd1/chemistry/pharma/comm.htm

NOTE

Because of the size of this presentation, this file comprises only the 4th (and last) part of the entire PPCPs slide presentation. The other three parts must be accessed separately.

Questions?

feel free to contact:

Christian Daughton, Ph.D.
Chief, Environmental Chemistry Branch
Environmental Sciences Division
National Exposure Research Laboratory
U.S. Environmental Protection Agency
daughton.christian@epa.gov
702-798-2207

http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm